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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,677	07/27/2000	Ole Isacson	04843/080001	2582

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EXAMINER
BAKER, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 05/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/626,677	ISACSON ET AL.	
	Examin r	Art Unit	
	Anne Baker	1632	

-- The MAILING DATE of this c mmunication appears on the cover she t with th corr spondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5+6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The response filed March 12, 2002 (Paper No. 8) has been entered.

Claims 1-11 are pending in the instant application.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The Post Office address is not provided for Ole Isacson. The Post Office address and residence address are not complete for Kwang Soo Kim.

At page 2 of the response, Applicants refer to the Declaration filed November 11, 2000 and Applicants provide with the response a copy of that Declaration. However, this is the defective declaration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-5 of the Office Action of Paper No. 4 (mailed 10/40/01) as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a human patient suffering from a neurodegenerative disease by engrafting into said patient a population of recombinant cells comprising one or more cell fate-inducing genes that permit said cells to form neurons in said patient.

At page 2, paragraph 4, Applicants argue that the Examiner has misapprehended the nature of the claimed invention. Applicants argue that the invention does not relate to the field of gene therapy and that it is exclusively related to the field of cell therapy. Applicants further argue, at page 3, paragraph 3, that although the transplanted cells are modified by the *ex vivo* insertion of a heterologous gene, the therapeutic benefit of transplantation does not depend on the continued expression of an inserted gene. However, the Examiner does not agree that the invention is unrelated to gene therapy, as the specification explicitly contemplates using the claimed invention in an *ex vivo* gene therapy approach. The specification states at page 18, paragraph 1, that TESCs (totipotent embryonic stem cells) may be used to deliver therapeutic proteins into the brain of patients with neurodegenerative disorders. The claims call for the transplantation of **recombinant** cells. Thus, the claimed subject matter relates to *ex vivo* gene therapy. Furthermore, even where there is no need or requirement to deliver therapeutic proteins to the brain and the invention is construed as cell therapy, it still depends on the *in vivo* expression of exogenous DNA. Genetically modified cells (particularly embryonic stem cells) are transplanted to the brain. Therefore, the state of the art in the field of *ex vivo* gene therapy is pertinent in evaluating enablement of the claimed invention. The transplanted cells must express the exogenous DNA to produce replacement neurons at the critical locations. Furthermore, these replacement neurons must have the appropriate phenotype necessary to correct the deficiency caused by the neurodegenerative disease. With regard to Parkinson's disease (PD), the art teaches that these replacement neurons should be dopaminergic neurons. However, the specification does not teach the neuronal phenotype required to treat any other type of neurodegenerative disease. Moreover, the specification does not teach how to practice the claimed method to produce replacement neurons of the desired phenotype at the critical locations through the *in*

vivo differentiation of embryonic stem (ES) cells transplanted into the brain. These replacement neurons must also integrate into the tissues in a functional manner. The specification contemplates that transfecting the ES cells with one transcription factor gene or the right combination of several transcription factor genes will be sufficient to direct the cells to differentiate *in vivo* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

At page 4, paragraph 3 of the response, Applicants argue that there is no requirement to teach what is already known in the art. At paragraph 4, Applicants argue that the transplantation of human fetal dopaminergic neurons was already known in the art. However, the cells being used in the instantly claimed method are very different from cells that have already terminally differentiated into dopaminergic neurons. The claimed method uses undifferentiated genetically modified ES cells which must undergo differentiation *in vivo* to produce the appropriate cell type for the treatment of the disease that is present in the patient. Therefore, the claimed method does not involve what is already known in the art because the claimed method does not involve the transplantation of fetal dopaminergic neurons or even dopaminergic neurons.

At page 5, paragraph 3 of the response, Applicants argue that working examples are not a requirement for enablement. However, lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. MPEP 2164.02.

At page 5, paragraph 4 of the response, Applicants argue that human testing is not required, for enablement purposes, to support claims of an *in vivo* utility. Applicants appear to be addressing a

rejection that was never made. The Examiner agrees that human testing is not required. However, the examples presented in the specification do not constitute working examples because they do not correlate with the claimed method. The MPEP discusses the issue of correlation, stating that

> "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example correlates with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute 'working examples.'" (MPEP 2164.02)

Example 4 of the specification describes the transplantation of murine ES cells into mice and rats, but no results are provided with regard to engraftment, functional integration, or amelioration of clinical symptoms. Furthermore, it is unclear if the transplanted cells were genetically modified cells. Example 6 of the specification describes the transfection of human ES cells with the β-galactosidase gene. Although the disclosure states that "[s]taining for expression of the β-galactosidase marker gene was performed," no results are provided with regard to the detection of β-galactosidase-expressing cells. In view of the MPEP guidance, these examples do not constitute working examples.

At page 6, paragraph 4 of the response, Applicants argue that the prior art, combined with the teachings of the specification, provides an expectation of success. However, as discussed above, prior art successes in the transplantation of neural tissue for the treatment of neurodegenerative disease is limited to the transplantation of fetal dopaminergic neurons. The claimed method uses a very different cell type, namely undifferentiated ES cells, with different characteristics.

At page 7, paragraphs 1-3 of the response, Applicants argue that Jackowski teaches that the transplanted fetal tissue is not growth restricted in the adult nervous system. Applicants assert that the transplanted cells of the present invention have many characteristics of fetal cells. However, no support is offered for this statement and it is unclear to the Examiner what characteristics undifferentiated ES cells share with fully differentiated fetal dopaminergic neurons.

At page 8, paragraph 2 of the response, Applicants assert that the transplanted cells will ultimately become fully differentiated into the selected cell type and fully integrated into the nervous

tissue where they will assume the function of the lost cells. No support is offered for this assertion and, given that local environment plays an important role in both the differentiation of stem cells and the survival and integration of transplanted cells into neural tissue (Jackowski, p. 311, column 1), it is unclear how the genetically modified ES cells will function *in vivo*.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of diseases covered, and the unpredictability for achieving a therapeutic effect upon the transplantation of ES cells, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-11 are indefinite in their recitation of "cell fate-inducing genes" because this term is not defined in the specification and therefore the metes and bounds are not clearly set forth.

At page 9, paragraph 4 of the response, Applicants point to the specification for teaching that the cell fate inducing genes cause the cells to form dopaminergic neurons, in a preferred embodiment. However, it is unclear if the "cell fate inducing gene" only relates to cell type or if it also relates to phenotype of the cells. Here, the disclosure refers to "dopaminergic neurons." If a "cell fate inducing gene" confers a particular phenotype to a cell, then virtually any gene would constitute a "cell fate inducing gene." The sections of the specification to which Applicants point provide only non-limiting

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Anne-Marie Baker, Ph.D.

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER